The Application concerns the following changes:

- Change in the ratio of carbidopa/levodopa combination from 1:10 to 1:4;
- Change of the anticholinergic from biperiden to trihexyphenidyl;
- Adding a dopamine agonist (pramipexole);
- Adding a selective MAO B inhibitor (selegiline);
- Adding amantadine to treat dyskinesias.

### 1. Assessment of efficacy

a. Have all relevant studies on efficacy been included
   - First two changes are motivated mainly by availability issues, although PK and tolerability data may also support the change of carbidopa/levodopa ratio.
   - The next three refer to the relevant Cochrane reviews, but provide relatively limited data on comparative effectiveness of these therapies.

b. Summarize the data on efficacy, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

As concluded by the authors of the Cochrane reviews:

As monotherapy or as an adjunct to other antiparkinsonian drugs, anticholinergics are more effective than placebo in improving motor function in Parkinson’s disease. Neuropsychiatric and cognitive adverse events occur more frequently on anticholinergics than on placebo and are a more common reason for withdrawal than lack of efficacy. Results regarding a potentially better effect of the anticholinergic drug on tremor than on other outcome measures are conflicting and data do not strongly support a differential clinical effect on individual parkinsonian features. Data is insufficient to allow comparisons in efficacy or tolerability between individual anticholinergic drugs.

Motor complications are reduced with dopamine agonists compared to levodopa, but other important side-effects are increased and symptom control is poorer with agonists. Larger, long-term comparative trials assessing patient-rated quality of life are needed to assess more reliably the balance of benefits and risks of dopamine agonists compared to levodopa.

MAO-B inhibitors are one option for the early treatment of PD although they have weaker symptomatic effects than levodopa and dopamine agonists. They may reduce the rate of motor fluctuations compared with initial levodopa therapy and may have fewer significant adverse effects than the older agonists but data are too few to provide reliable conclusions.
Due to lack of evidence it is impossible to determine whether amantadine is a safe and effective form of treatment for levodopa-induced dyskinesias in patients with Parkinson’s disease.

c. Please provide any additional relevant information with reference


2. Assessment of safety
   a. Have all relevant studies on safety been included
      Yes ✓
   b. Summarize the data on safety, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

      See Cochrane conclusions above.

c. Please provide any additional relevant information with reference

NA

3. Assessment of cost and availability
   a. Have all relevant data on cost provided
      No ✓
   b. Summarize the data on cost and cost effectiveness, in comparison to what is listed in EML where applicable (limit to 2 to 3 sentences)

      Cost data have been provided as follows:

      | Year of treatment                                    | Cost  |
      |------------------------------------------------------|-------|
      | Year of treatment with a levodopa product             | USD 300 |
      | Year of treatment with a trihexyphenidyl product      | £ 170  |
      | Year of treatment with a pramipexole product          | £ 786  |
      | Year of treatment with an amantadine product          | £ 17   |
      | Year of treatment with a selegiline product           | £ 104  |

      Estimates do not seem to be very precise or to reflect a range of countries. No formal cost-effectiveness data have been submitted.

c. Please provide any additional relevant information with reference

Relative effectiveness and cost-effectiveness in countries with different income levels need to be assessed before additions to the list can be decided upon.


d. Is the product available in several low and middle income countries?

Yes ✓

4. Assessment of public health need

a. Please provide the public health need for this product (1-2 sentences)

Parkinson’s Disease is of high and increasing prevalence and at the same time an effectively symptomatically treatable condition. No single therapy is suitable for all patients throughout the course of the disease, although the levodopa combinations are the cornerstone of the therapy. Therefore the better access to the selection of effective PD therapies is of high public health importance.

b. Do guidelines (especially WHO guidelines) recommend this product? If yes, which ones? List 1 or 2 international preferable

Most current guidelines would describe/support the use of the following drug classes:

– Levodopa
– MAO B inhibitors
– Dopamine agonists
– COMT inhibitors – in motor complications
– Anticholinergic agents – limited evidence
– Amantadine – limited evidence


5. Are there special requirements for use or training needed for safe/effective use?

Not for the first line treatment of early disease. Access to neurologist service would be highly beneficial for the treatment of advanced disease and motor complications.
6. Is the proposed product registered by a stringent regulatory authority?
Yes ✓

7. Any other comments

The proposal for addition of several drug classes should perhaps be seen as a start for further evaluation.

8. What is your recommendation to the committee (please provide the rationale)

– Based on the application, the change in the recommended ratio of the carbidopa/levodopa combination to 1:4 should be supported.
– Similarly, the change/addition of the anticholinergic (trihexyphenidyl ) can be supported, although the availability of the specific representatives of this class may be region dependent.
– Addition of a non-ergot DA agonist, MAO B inhibitor and amantadine merit further effectiveness and pharmacoeconomic evaluation before a decision can be taken.